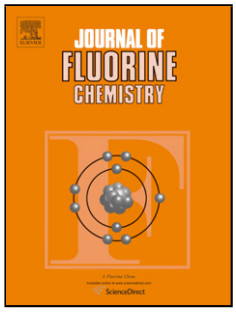

Title: Cobalt/diamine-Catalyzed 1,1-Difluoroethylation and 2,2,2-Trifluoroethylation of Aryl Grignard Reagents with Corresponding Fluoroalkyl Halides

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Cobalt/diamine-Catalyzed 1,1-Difluoroethylation and 2,2,2-Trifluoroethylation of Aryl Grignard Reagents with Corresponding Fluoroalkyl Halides

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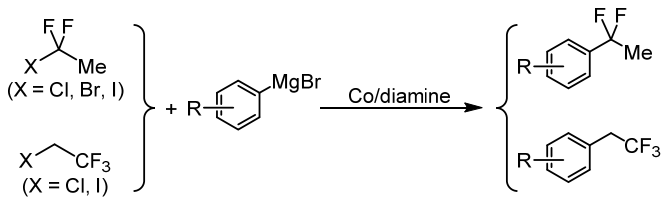
Graphical Abstract (pictogram)



Synopsis

The combined use of Co/diamine catalyzed 1,1-difluoroethylation and 2,2,2-trifluoroethylation of aryl Grignard reagents with 1,1-difluoroethyl and 2,2,2-trifluoroethyl halides, providing the desired products in satisfactory yields.

Highlights

・1,1-Difluoroethylation and 2,2,2-trifluoroethylation of ArMgBr proceeded smoothly.

・Co/diamine-catalyst showed the satisfactory activity in this reaction.

・The choice of diamine ligand and solvent are very important for excellent yields.

Abstract

Cobalt/diamine-catalyzed 1,1-difluoroethylation and 2,2,2-trifluoroethylation of aryl Grignard reagents with 1,1-difluoroethyl and 2,2,2-trifluoroethyl halides were investigated. With regard to the 1,1-difluoroethylation, 1,2-bis(dimethylamino)-2-methylpropane, which has been rarely used in the cross-coupling reactions, gave the highest yield among the diamine ligands tested. In the 2,2,2-trifluoroethylation, *trans*-1,2-bis(dimethylamino)cyclohexane provided the desired products in satisfactory yields with not only 2,2,2-trifluoroethyl iodide but also chloride. This Co/diamine catalyst was also effective for the coupling with other partially fluorinated alkyl halides in the presence of appropriate diamine ligands.

Keywords: 1,1-difluoroethylation; 2,2,2-trifluoroethylation; cobalt catalyst; diamine ligand

1. Introduction

Because trifluoromethyl and difluoromethyl groups directly bound to aromatic rings give unique bio-active character, numerous syntheses of aromatic compounds containing these functional groups have been reported [1,2]. In a similar manner, other fluoroalkyl groups, particularly partially fluorinated alkyl groups, have received much attention for medical and agricultural compounds [3]. Recently, the remarkable bioactivity of heteroaromatic compounds and nucleobases featuring the 1,1-difluoroethyl (CH_3CF_2) group, which mimics the steric and electronic features of methoxy group [4b-e], has been explored [4]. Thus far, aromatic compounds having CH_3CF_2 group have been synthesized *via* fluorination of functional groups on aromatic rings with various fluorinating reagents. Fluorination of the ethynyl group in phenylacetylene using HF-organic base provides 1,1-difluoroethylbenzene [5]. Deoxo-Fluor (bis(2-methoxyethyl)aminosulfur trifluoride) [6] or phenylsulfur chlorotetrafluoride [7] converts the acetyl group in acetophenone to CH_3CF_2 group, yielding 1,1-difluoroethylbenzene. Similarly, 3-acetylindoles were converted to 3-(1,1-difluoroethyl)indoles with DAST (*N*,*N*-diethylaminosulfur trifluoride) [8]. The use of Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) [9] or uranium hexafluoride [10] gives 1,1-difluoroethylbenzenes from 2-methyl-2-phenyl-1,3-dithiolane or 2-aryl-1,3-dithianes. The methylene hydrogen atoms in ethylbenzenes can be selectively substituted with fluorine atoms by using Selectfluor or Selectfluor II (4-fluoro-1-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) in the presence of a catalytic amount of xanthone [11a] or $Na_2S_2O_8$ [11b,c]. Very recently, fluorination of (1-chloroethenyl)benzene or 1-bromo-4-(1-chloroethenyl)benzene with HF to (1,1-difluoroethyl)benzene or 1-bromo-4-(1,1-difluoroethyl)benzene, respectively, was reported in a patent [12]. This method appears to be more practical than the other ones, because HF is the most inexpensive fluorinating reagent.

On the other hand, 1,1-difluoroethylation of aromatic compounds *via* cross-coupling using 1,1-difluoroethyl halides [13] or their metal reagents has not been reported to the best of our knowledge, although it requires no toxic and expensive fluorination reagents. In particular, the

cross-coupling of 1,1-difluoroethyl halides and arylmetal reagents can be a practical and usable process because of its availability of substrates.

With regard to 2,2,2-trifluoroethylation, which furnishes bioactive aromatic compounds possessing the 2,2,2-trifluoroethyl (CF_3CH_2) group [14], several examples of palladium-catalyzed cross-couplings of 2,2,2-trifluoroethyl iodide or triflate and arylboronic acids or their esters have been reported [15]. However, they require a large amount of palladium, expensive ligands such as 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl and optionally CuCl. Xu and co-workers reported the Cu-promoted coupling of aryliodides 2,2,2-trifluoroethyl iodide [16]. Although this reaction proceeds without any ligands and bases, the excess amount of Cu powder and the long reaction time, 55 h, are necessary. Recently, Ackermann and co-workers showed 2,2,2-trifluoroethylation with CF_3CH_2I through C-H bond activation with a catalyst consisting of [(dimethoxyethane)$NiCl_2$] and bis(2-dimethylaminoethyl)ether [17], though the substrates of this reaction were limited to benzamides and 2,2,2-trifluoroethylation occurred only at the *ortho* position of an amide group. In addition, the radical 2,2,2-trifluoroethylation of aromatic C-H bond with zinc (2,2,2-trifluoroethyl)sulphinate afforded only 15% yields [18].

We began our investigation with the aim of realizing a more general and practical cross-coupling process for partially fluorinated alkylation. Therefore, we focused on a catalyst consisting of cobalt and a diamine ligand that catalyzes the cross-coupling of aryl Grignard reagents and alkyl halides [19] or arylzinc reagents and ethyl bromodifluoroacetate [20]. As a result, we found that 1,1-difluoroethylation and 2,2,2-trifluoroethylation proceeded smoothly with readily available 1,1-difluoroethyl iodide (CH_3CF_2I), 1,1-difluoroethyl bromide (CH_3CF_2Br) or 2,2,2-trifluoroethyl iodide (CF_3CH_2I) and aryl Grignard reagents in the presence of a Co/diamine catalyst. Interestingly, 2,2,2-trifluoroethylation also occurred by the use of corresponding chloride (CF_3CH_2Cl), which should be rather inactive. Based on the other partially fluorinated alkylation by the use of partially fluorinated alkyl halides possessing three or four carbons, we revealed that the yields largely depended on the diamine ligand.

2. Results and discussion

2.1 1,1-Difluoroethylation

Scheme 1 illustrates the reaction of 4-methoxyphenyl Grignard reagent and CH_3CF_2I with $CoCl_2$ as a cobalt precursor and *trans*-1,2-bis(dimethylamino)cyclohexane (ligand **a**) or *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as a diamine ligand; these diamine ligands were used in the previously reported cobalt-catalyzed cross-coupling [19, 20]. The desired product was obtained in 40% and 80% ^{19}F NMR yield, respectively. This result indicated that the cobalt/diamine catalyst could be used for the target reaction and that surveying the reaction conditions to obtain the higher yields was worthwhile.

First, the reaction with 4-methoxyphenyl Grignard reagent was examined with various cobalt precursors and diamine ligands. CH_3CF_2Br was used in this examination instead of the iodide, because (i) it is less expensive than the iodide, and (ii) the differences derived from the precursors and ligands could be clearer owing to its lower reactivity compared to the iodide. Taking into account the low boiling point (14 ºC) of CH_3CF_2Br, the reactions were carried out with a THF solution of the bromide. Table 1 lists the results obtained using various cobalt precursors with ligand **a** that gave the higher yield in Scheme 1. As anticipated from the reactivity of the bromide, the yield with $CoCl_2$ decreased to 62%, which was lower than that with the bromide, 80% (entry 1). Of the cobalt halides tested, CoI_2 provided the highest yield of the desired product (entry 3). Both divalent and trivalent fluoride salts were inactive (entries 4 and 5). A divalent acetate precursor gave a moderate yield (entry 6). With regard to acetylacetonate precursors, both divalent and trivalent precursors provided moderate yields (entries 7 and 8). When 0.05 mmol of CoI_2, $CoBr_2$ or $CoCl_2$ and ligand **a** were used, all the yields decreased (entries 9-11) and a satisfactory yield, 74%, was obtained only with CoI_2. Based on the results in Table 1, 0.10 mmol of $CoCl_2$ was chosen as the precursor hereinafter, because it gave a satisfactory yield and was readily available.

Figure 1 shows the ^{19}F NMR yields of 1-(1,1-difluoroethyl)-4-methoxybenzene from CH_3CF_2Br and 4-methoxyphenyl Grignard reagent with $CoCl_2$ and various diamines featuring an *N,N,N',N'*-tetramethylethylenediamine backbone as a ligand. Although the yield with ligand **a** was larger than that with TMEDA, each ligand afforded a lower yield than Scheme 1. This is readily anticipated by the lower reactivity of bromide than iodide. Interestingly, only 1,2-bis(dimethylamino)-2-methylpropane (ligand **b**) gave a higher yield than ligand **a** (89% *vs.* 62%) among the diamines tested. This compound is known as a catalyst in polyurethane synthesis [21] and is one of the ligands in $LiNEt_2$-catalyzed hydroamination [22]. However, it has never been used in cross-coupling reactions to the best of our knowledge. All of the other diamine ligands also afforded lower yields than ligands **a** and **b**. In addition, bis(2-dimethylaminoethyl)ether, which was used in the nickel-catalyzed 2,2,2-trifluoroethylation through C-H bond activation afforded no desired product at all.

Based on the results in Table 1 and Figure 1, we chose ligand **a** (*trans*-1,2-bis(dimethylamino)cyclohexane), which has been used previously in the cobalt-catalyzed cross-coupling, and ligand **b** (1,2-bis(dimethylamino)-2-methylpropane), which revealed its availability in cross-coupling reactions in the present investigation, for the survey of the reaction conditions.

Next, we examined the use of oligoethers as a solvent for $CoCl_2$ and the ligand in the coupling of CH_3CF_2Br and 4-methoxyphenyl Grignard reagent. Table 2 lists the ^{19}F NMR yields using ligands **a** and **b** in ethylene glycol dimethylether (DME), diglyme and triglyme solvents. In the reactions with ligand **a**, the yield rose up to 92% in diglyme solvent (entry 3), while the use of DME and triglyme as a solvent afforded similar yields to THF (entry 1 *vs.* 2 and 4). Diglyme is well known to enhance the nucleophilicity of a Grignard reagent through bidentate coordination to magnesium [23]. Therefore, it is reasonable that the activation of 4-methoxyphenyl Grignard reagent brought about the excellent yield. In contrast, the yields obtained using ligand **b** were lower with each oligoethers. It is well known that oligoethers also act as polydentate ligands to cobalt [24]. Thus far, the syntheses of several kinds of Co(II) complexes featuring the oligoethers in Table

2, DME [24a-c], diglyme [24c-e] and triglyme [24f] and a chloride ligand were reported. This suggests that the decrease in the yields with ligand **b** may be due to the change in the cobalt species through the substitution of ligand **b** with the oligoethers. Therefore, we noted the colors of the solutions of each reaction in Figure 1 and Table 2. The solutions of each reaction in Figure 1, except bis(2-dimethylaminoethyl)ether, were dark blue, indicating that bidentate coordination of each diamine ligands to Co(II) [25]. The reaction solution containing bis(2-dimethylaminoethyl)ether was purple, which was consistent with the report that [Co(bis(2-dimethylaminoethyl)ether)Cl_2] was purple [26]. The solutions of each reaction in Table 2 were also dark blue. On the other hand, the color of the isolated Co(II) complexes featuring the oligoethers, which ranges between blue and purple [22], is very similar to that of Co(II) complexes coordinated with TMEDA derivatives. Therefore, it is difficult to estimate the change in the cobalt species by observing the colors of the reaction solutions.

Next we attempted the reaction using 1,1-difluoroethyl chloride (CH_3CF_2Cl), which is generally less active than CH_3CF_2Br (Table 3). Indeed, the yield with CH_3CF_2Cl was remarkably lower than with CH_3CF_2Br using ligand **a** (entry 1). Keeping the reaction solution at 40 ºC during the addition of the THF solution of the Grignard reagent and the use of diglyme improved the yield to 60% (entry 3), which was almost the same as entry 1 in Table 1 (62%). Ligand **b** afforded a lower yield with CH_3CF_2Cl than with CH_3CF_2Br (entry 4) even when the reaction was performed at 40 ºC.

Table 4 lists the yields of 1,1-difluroethylation of various aryl Grignard reagents with CH_3CF_2Br. Both ligand **a** in diglyme and **b** in THF provided the desired products from each substrate in satisfactory yields except 2-methoxyphenyl Grignard reagent (entry 3). In particular, 4-(1,1-difluoroethyl)biphenyl was obtained quantitatively with both ligands (entry 7). The yields in entries 1 and 6 with electron-donating substituents and those in entries 8 and 9 with electron-withdrawing substituent were all satisfactory. In addition, the reactions with phenyl Grignard reagent also gave the similar yields (entry 4). This suggests that the electronic character of

substituents did not affect the yield. The rather low yield in entry 3 is presumably due to steric hinderance by the methoxy group at the *ortho* position.

All the products in Table 4 could be isolated by the general procedure (see 4.2. Reaction procedure). The isolated yields in Table 4 except entry 5 and 7 were rather lower than the ^{19}F NMR yields presumably due to volatility derived from the existence of fluorine atoms. In particular, drastic decline in the isolated yield was observed with 1,1-difluoroethylbenzene that has small molecular weight (entry 4) and 1-(1,1-difluoroethyl)-4-trufluoromethylbenzene that has five fluorine atoms (entry 9).

2.2 2,2,2-Trifluoroethylation

First, the coupling of CF_3CH_2I and 4-methoxyphenyl Grignard reagent using $CoCl_2$ and ligand **a** or **b** was investigated; the use of 2,2,2-trifluoroethyl bromide is legally prohibited. The results are listed in Table 5. The yield with ligand **a** under the same conditions as entry 3 in Table 2, in diglyme, was 72% yield (entry 1). When the reaction temperature was lowered to 0 ºC, the yield was slightly improved (entry 2). Interestingly, the yield at 0 ºC reached 92% in THF (entry 3). This is in remarkable contrast to the result in difluoroethylation. The 62% yield of entry 1 in Table 1, in THF, decreased drastically to 7% at 0 ºC. The yield with ligand **b** was also higher at 0 ºC than at room temperature (entry 4 *vs.* 5), though it was lower than with ligand **a**. Similar satisfactory yields to those obtained with ligand **b** were obtained with TMEDA and 1,2-bis(dimethylamino)propane which afforded low yields in the reactions with CH_3CF_2Br (Figure 1).

Next, we examined the 2,2,2-trifluoroethylation using CF_3CH_2I and 2,2,2-trifluoroethyl chloride (CF_3CH_2Cl) with various aryl Grignard reagents. Each substrate gave the desired product in a satisfactory yield (Table 6). We found two differences between 1,1-difluoroethylation and 2,2,2-trifluoroethylation in the results in Table 6. One is the satisfactory yield with 4-(dimethylamino)phenyl Grignard reagent (entry 6), which afforded no product in the 1,1-difluoroethylation. The other is the unexpected high reactivity of CF_3CH_2Cl. While all of the yields obtained in 2,2,2-trifluoroethylation with the chloride were slightly lower than those with the

idodide, 1,1-difluoroethylation with CH_3CF_2Cl required a higher reaction temperature than with CH_3CF_2Br to obtain satisfactory yields (Table 1 *vs*. Table 3). Similar to the products in Table 4, the compounds bearing 2,2,2-trifluoroethyl group are certainly volatile, resulting in low isolated yields.

Since it is generally recognized that cobalt-catalyzed cross-coupling with alkyl halides involves alkyl radical formation from the corresponding halides [27], the difference between 2,2,2-trifluoroethylation and 1,1-difluoroethylation should be derived from the difference in the property between 2,2,2-trifluoroethyl radical and 1,1-difluoroethyl radical. We now investigate the properties of the radicals from the standpoints of difficulty in generation, stability, reactivity and other factors using various partially fluorinated alkyl halides.

2.3 Other partially fluorinated alkylation

Finally, we attempted the cobalt/diamine-catalyzed coupling of 2,2-difluoroethyl-, 2,2,3,3-tetrafluoro-*n*-propyl- or 2,2,3,3,3-pentafluoro-*n*-propyl iodide and 4-methoxyphenyl Grignard reagent. Table 7 shows the diamine ligands that provided the highest and the second highest yields for each iodide in screening of diamine ligands in THF. The results revealed that (i) 2,2-difluoroethylation proceeded more smoothly with 1-[(1-methylpyrrolidine-2-yl)methyl]piperidine, which afforded a rather poor yield in 1,1-difluoroethylation (Figure 1), than with ligand **a** (entry 1 *vs.* 2), (ii) the highest yields with the latter two iodides were obtained with ligand **a** (entries 4 and 6), and (iii) TMEDA also provided the satisfactory yields from latter two iodides despite slightly lower than ligand **a**. Surprisingly, ligand **b** afforded lower yields with any of the iodides than these diamine ligands. These results indicate that the choice of diamine ligand is very important in the present reaction, including 1,1-difluoroethylation and 2,2,2-trifluoroethylation. The isolated yields of products in Table 7 are also rather lower than ^{19}F NMR yield due to their volatility as well as those in Table 4 and 6.

3. Conclusion

In this study, we revealed that the cobalt/diamine-catalyzed 1,1-difluoroethylation and

2,2,2-trifluoroethylation of aryl Grignard reagents proceeded smoothly with the corresponding halides. Moreover, other partially fluorinated alkylations provided the desired products with the cobalt/diamine catalyst. The choice of diamine ligand and solvent are very important for excellent yields. Because the present method is simple and uses an inexpensive catalyst, we believe that it has a potential as a practical process.

4. Experimental

4.1. General techniques

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-500 (^{13}C 125 MHz) and a DRX-250 (^{1}H 250 MHz, ^{19}F 235 MHz) spectrometers using tetramethylsilane as an internal reference for ^{1}H and ^{13}C NMR, and fluorotrichloromethane as an external reference for ^{19}F NMR. The chemical shifts are expressed in ppm (δ). The multiplicities are indicated as brs (broad singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplet), tt (triplet of triplet) and m (multiplet). The ^{19}F NMR yields were calculated using benzotrifluoride as an internal standard. IR and high-resolution mass spectroscopy (HR-MS) were measured using a HORIBA FT-720 and a JMS-T100LP AccTOF LC-plus 4G, respectively. IR spectra were obtained in the reflective mode. All of the commercially available reagents were used without further purification. According to a literature method [28], CH_3CF_2I was synthesized from 1,1-difluoroethylene and trifluoromethanesulfonic acid as starting materials.

4.2. Reaction procedures

The procedure for the synthesis of 1-(1,1-difluoroethyl)-4-methoxybenzene (entry 1 in Table 1) is used as a representative example. A 2.0 mL THF solution containing 13.0 mg of $CoCl_2$ (0.10 mmol) and 17.0 mg of *trans*-1,2-bis(dimethylamino)cyclohexane (0.10 mmol) was prepared. This solution was added to 1.0 mL of a 1.0 mol/L 1,1-difluoroethyl bromide in THF (1.0 mmol) in a reaction vessel under an argon atmosphere and the mixture was stirred for 15 min at room temperature. To this reaction mixture, 4.2 mL of a 0.36 mol/L bromo(4-methoxyphenyl)magnesium

solution in THF (1.5 mmol) was added dropwise at a rate of 2.1 mL/h for 2 h at room temperature. The mixture was further stirred for 1 h at room temperature. After the reaction, saturated NH_4Cl aqueous solution (2.5 mL) and H_2O (2.5 mL) were added to the obtained mixture and the product was extracted with diethyl ether (3 mL × 3). ^{19}F NMR analysis of the diethyl ether layer with benzotrifluoride as an internal standard revealed that the yield of 1-(1,1-difluoroethyl)-4-methoxybenzene was 92% based on the charged amount of 1,1-difluoroethyl bromide. The isolation of the product was performed through the following procedure. After the addition of a saturated NaCl aqueous solution (5 mL), the diethyl ether layer was dried with anhydrous Na_2SO_4. Na_2SO_4 was removed by filtration, and the filtrate was concentrated *in vacuo*. The obtained crude product was purified by the use of silica gel column chromatography (eluent hexane/ethyl acetate = 15/1), providing 1-(1,1-difluoroethyl)-4-methoxybenzene as a colorless oil in 61% yield (105 mg).

4.3 Characterization of products

Following 5 compounds are new and NMR (^1H, ^{13}C and ^{19}F), IR and HR-MS data of them are shown below. The other compounds are known and the characterization data of ^1H, ^{13}C or ^{19}F NMR agreed with the reported data.

4.3.1. 1-(1,1-difluoroethyl)-3-methoxybenzene

colorless oil. ^1H NMR ($CDCl_3$) δ 1.91 (t, J_{HF} = 18.1 Hz, 3H), 3.84 (s, 3H), 6.93-6.98 (m, 1H), 7.02-7.05 (m, 1H), 7.06-7.11 (m, 1H), 7.30-7.36 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 25.8 (t, J_{CF} = 29.9 Hz), 55.1, 110.3 (t, J_{CF} = 6.3 Hz), 115.1, 116.8 (t, J_{CF} = 6.1 Hz), 121.6 (t, J_{CF} = 239.1 Hz), 129.6, 139.6 (t, J_{CF} = 26.6 Hz), 159.6. ^{19}F NMR ($CDCl_3$) δ –87.6 (q, J_{FH} = 18.1 Hz). IR (neat) 1587, 1456, 1302, 1234, 1173, 1045, 926, 783, 698 cm^{-1}. HR-MS: calcd for $C_9H_{11}F_2O$ (M+H): 173.0772; found: 173.0801.

4.3.2. 1-(1,1-difluoroethyl)-4-methylbenzene

colorless oil. ^1H NMR ($CDCl_3$) δ 1.91 (t, J_{HF} = 18.1 Hz, 3H), 2.38 (s, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.2, 25.9 (t, J_{CF} = 30.2 Hz), 122.0 (t, J_{CF} = 238.4 Hz), 124.5 (t, J_{CF} = 6.1 Hz), 129.1, 135.4 (t, J_{CF} = 26.6 Hz), 139.6. ^{19}F NMR ($CDCl_3$) δ –86.9 (q,

J_{FH} = 18.1 Hz). IR (neat) 1383, 1296, 1173, 1111, 1088, 914, 818, 721 cm^{-1}. HR-MS: calcd for $C_9H_{11}F_2$ (M+H): 157.0823; found: 157.0836.

4.3.3. 1-(2,2-difluoroethyl)-4-methoxybenzene

colorless oil. ^1H NMR ($CDCl_3$) δ 3.07 (dt, J = 4.6 Hz, J_{HF} = 17.4 Hz, 2H), 3.80 (s, 3H), 5.87 (tt, J = 4.6 Hz, J_{HF} = 56.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 39.9 (t, J_{CF} = 21.8 Hz), 55.1, 114.0, 116.8 (t, J_{CF} = 241.2 Hz), 124.4 (t, J_{CF} = 6.0 Hz), 130.8, 159.0. ^{19}F NMR ($CDCl_3$) δ –115.0 (dt, J_{FH} = 56.7, 17.4 Hz). IR (neat) 1614, 1514, 1248, 1180, 1111, 1020, 820, 773 cm^{-1}. HR-MS: calcd for $C_9H_{11}F_2O$ (M+H): 173.0772; found: 173.0805.

4.3.4. 1-(2,2,3,3-tetrafluoropropyl)-4-methoxybenzene

colorless oil. ^1H NMR ($CDCl_3$) δ 3.22 (t, J_{HF} = 17.9 Hz, 2H), 3.81 (s, 3H), 5.68 (tt, J_{HF} = 3.4, 53.7 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 35.9 (t, J_{CF} = 22.7 Hz), 55.1, 110.0 (tt, J_{CF} = 249.4, 39.0 Hz), 114.1, 116.6 (tt, J_{CF} = 247.4, 28.2 Hz), 121.9 (t, J_{CF} = 3.5 Hz), 131.6, 159.3. ^{19}F NMR ($CDCl_3$) δ –115.9 (dt, JFH = 3.4, 17.9 Hz, 2F), –136.5 (d, J_{FH} = 53.7 Hz, 2F). IR (neat) 1614, 1514, 1248, 1099, 1034, 837, 777, 661 cm^{-1}. HR-MS: calcd for $C_{10}H_{11}F_4O$: 223.0741; found: 223.0761.

4.3.5. 1-(2,2,3,3,3-pentafluoropropyl)-4-methoxybenzene

colorless oil. ^1H NMR ($CDCl_3$) 3.26 (t, J_{HF} = 18.3 Hz, 2H), 3.81 (s, 3H), 6.89 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 36.2 (t, J_{CF} = 22.3 Hz), 55.1, 114.0, 114.6 (tq, J_{CF} = 251.9, 36.9 Hz), 119.3 (qt, J_{CF} = 285.7, 36.3 Hz), 121.0 (t, J_{CF} = 2.2 Hz), 131.7, 159.6. ^{19}F NMR ($CDCl_3$) δ –84.6 (s, 3F), –117.2 (t, J_{FH} = 18.3 Hz, 2F). IR (neat) 1614, 1516, 1244, 1188, 1026, 791, 696 cm^{-1}. HR-MS: calcd for $C_{10}H_{10}F_5O$: 241.0652; found: 241.0634.

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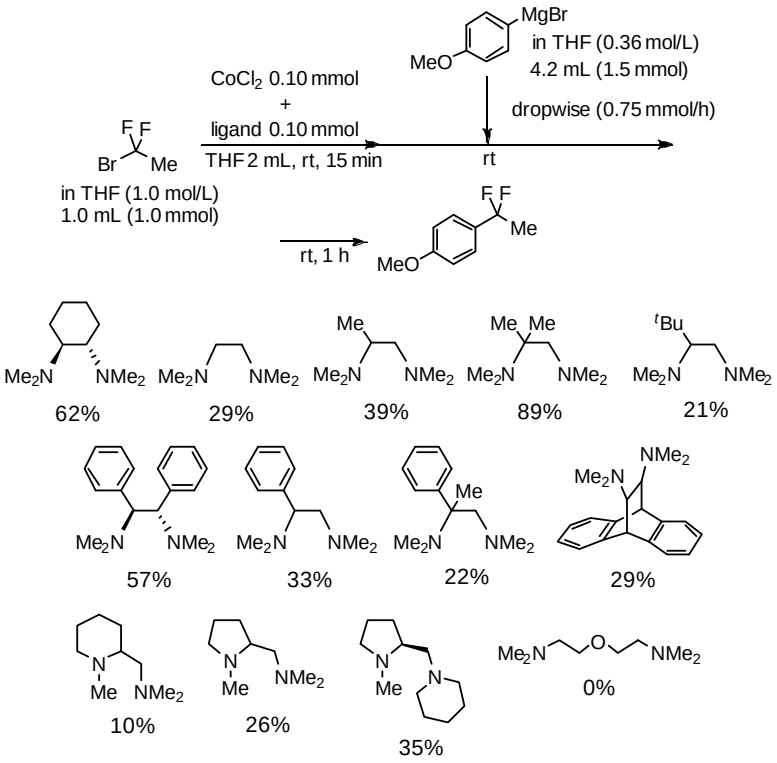
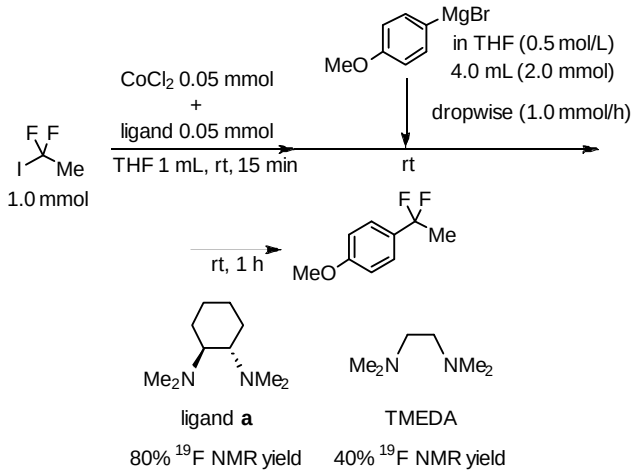


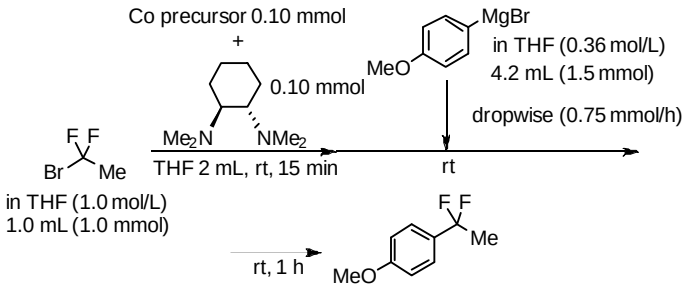
Figure 1 ^{19}F NMR yields of 1-(1,1-difluoroethyl)-4-methoxybenzene obtained through coupling of CH_3CF_2Br and 4-methoxyphenyl Grignard reagent with $CoCl_2$ and various diamine ligands



Scheme 1 Cobalt/diamine catalyzed coupling of CH_3CF_2I and 4-methoxyphenyl Grignard reagent

Table 1

Cobalt/diamine-catalyzed coupling of CH_3CF_2Br and 4-methoxyphenyl Grignard reagent with various Co precursors



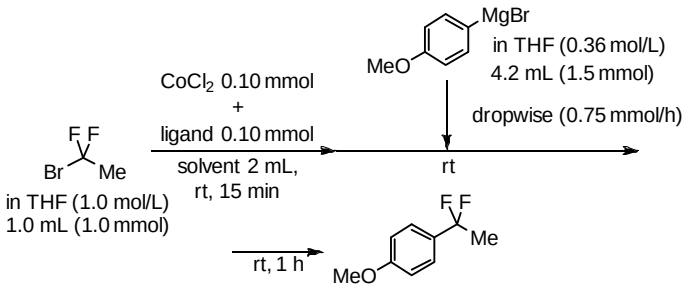
entry	Co precursor	yield / %[a]
1	$CoCl_2$	62
2	$CoBr_2$	67
3	CoI_2	79
4	CoF_2	2
5	CoF_3	3
6	$Co(OAc)_2$	55
7	$Co(acac)_2$	58
8	$Co(acac)_3$	40
9[b]	$CoCl_2$	52
10[b]	$CoBr_2$	54
11[b]	CoI_2	74

[a]Determined by ^{19}F NMR.

[b]Co precursor 0.05 mmol, ligand 0.05 mmol

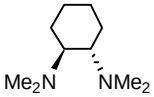
Table 2

Effect of oligoethers as a solvent in the cobalt/diamine catalyzed coupling of CH_3CF_2Br and 4-methoxyphenyl Grignard reagent

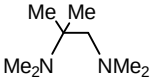


entry	solvent	yield / %[a]	
		ligand **a**	ligand **b**
1	THF	62	89
2	DME	56	80
3	diglyme	92	63
4	triglyme	67	60

[a]Determined by ^{19}F NMR.



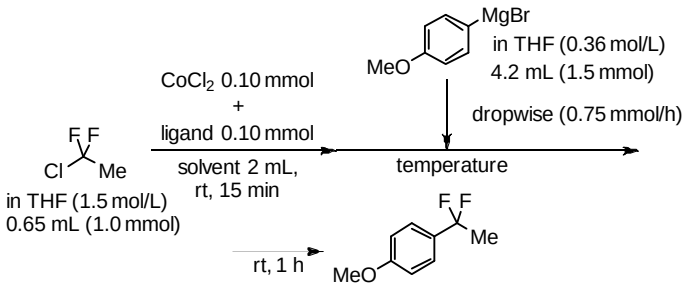
ligand **a**



ligand **b**

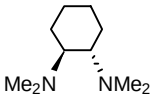
Table 3

Cobalt/diamine-catalyzed coupling of CH_3CF_2Cl and 4-methoxyphenyl Grignard reagent

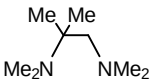


entry	ligand	solvent	temperature	yield / %[a]
1	**a**	THF	rt	11
2	**a**	THF	40 ºC	32
3	**a**	diglyme	40 ºC	60
4	**b**	THF	40 ºC	50

[a]Determined by ^{19}F NMR.



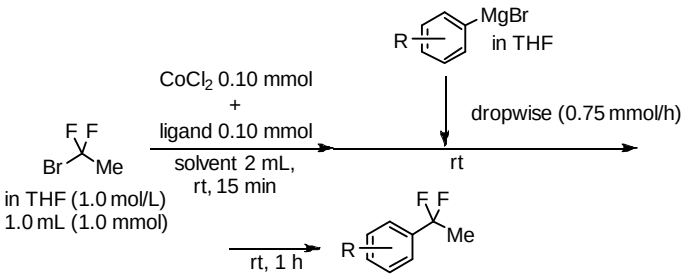
ligand **a**

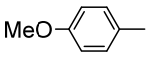
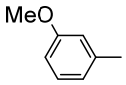
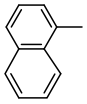
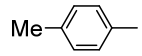
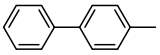
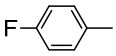
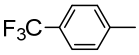


ligand **b**

Table 4

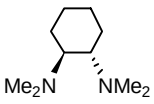
Cobalt/diamine-catalyzed coupling of CH_3CF_2Br and various aryl Grignard reagents



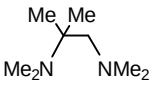
entry	R	yield / %[a]	
		ligand **a** in diglyme[b]	ligand **b** in THF
1		92 (61)	89 (57)
2		74 (49)	86 (55)
3		21 (8)	17 (9)
4		86 (28)	86 (20)
5		50 (41)	44 (38)
6		75 (38)	89 (21)
7		96 (93)	98 (95)
8		60 (33)	90 (32)
9		77 (22)	89 (22)

[a]Determined by ^{19}F NMR.

[b]Isolated yields were shown in parentheses.



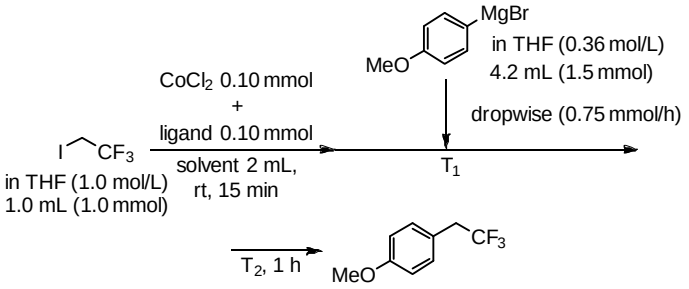
ligand **a**

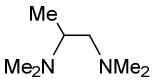


ligand **b**

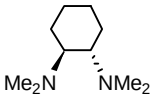
Table 5

Cobalt/diamine-catalyzed coupling of CF_3CH_2I and 4-methoxyphenyl Grignard reagent

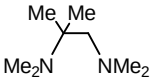


entry	ligand	solvent	T_1	T_2	yield / %[a]
1	**a**	diglyme	rt	rt	72
2	**a**	diglyme	0 ºC	0 ºC	77
3	**a**	THF	0 ºC	0 ºC	92
4	**b**	THF	rt	rt	39
5	**b**	THF	0 ºC	0 ºC	76
6	TMEDA	THF	0 ºC	0 ºC	77
7		THF	0 ºC	0 ºC	78

[a]Determined by ^{19}F NMR.



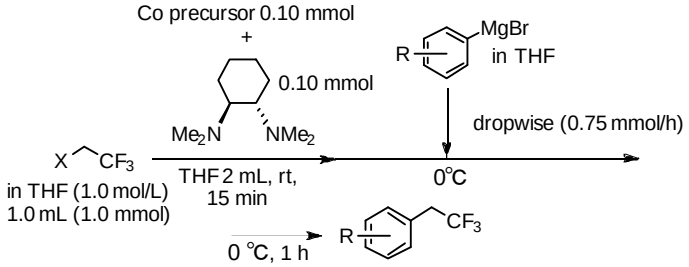
ligand **a**



ligand **b**

Table 6

Cobalt/diamine-catalyzed coupling of CF_3CH_2I or CF_3CH_2Cl and various aryl Grignard reagents



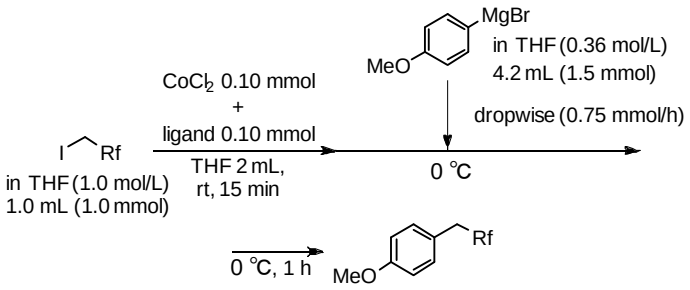
entry	R	yield / %[a]	
		X = I[b]	X = Cl
1	MeO	92 (46)	91 (53)
2	MeO	71 (41)	65 (42)
3		83 (25)	83 (32)
4	Me	71 (30)	69 (21)
5	F	77 (32)	71 (22)
6	Me_2N	86 (29)	78 (34)

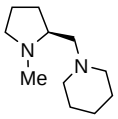
[a]Determined by ^{19}F NMR.

[b]Isolated yields were shown in parentheses.

Table 7

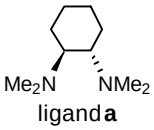
Cobalt/diamine-catalyzed coupling of various partially-fluorinated alkyl iodides and 4-methoxyphenyl Grignard reagents



entry	R_f	ligand	yield / %[a]
1	$-CF_2H$	**a**	89
2	$-CF_2H$		94 (62)[b]
3	$-CF_2H$	TMEDA	85
4	$-CF_2CF_2H$	**a**	96 (58)[b]
5	$-CF_2CF_2H$	TMEDA	83
6	$-CF_2CF_3$	**a**	75 (52)[b]
7	$-CF_2CF_3$	TMEDA	72

[a]Determined by ^{19}F NMR.

[b]Isolated yields were shown in parentheses.



ligand **a**